BOX AF
RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1644

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In re the Application of MOURITSEN et al.

Serial No.: 08/955,373 Group Art Unit: 1644

Filed: October 21, 1997 Examiner: R. Schwadron

For: INDUCING ANTIBODY RESPONSE AGAINST SELF-PROTEINS WITH THE AID OF FOREIGN T-CELL EPITOPES

RESPONSE

Box AF
Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

The instant paper responds to the Office Action mailed May 2, 2000.

Claims 26, 28-43, and 45-53 are pending.

Claims 29-43, 48, 51 and 52 were withdrawn pursuant to a restriction requirement.

Claims were rejected under 35 USC 112, ¶ for allegedly containing indefinite claim language. Reconsideration is respectfully requested.

The rejection is based on the allegation that the claim term "essentially preserve the overall tertiary structure" is indefinite. According to the statement of rejection, the claim term is indefinite because (Office action, page 2):

> It is unclear what changes to the tertiary structure would or would not be encompassed by the aforementioned term. For example, it is unclear if this term encompasses changes at the physical/chemical level (e.g., crystal structured [sic]) or simply functional changes (e.g. still immunogenic antigen as evidenced by antibody binding to

> antibodies specific for unmodified antigen). If the term is interpreted as encompassing changes at the physical/chemical level, it is unclear as to what deviations from the normal crystal structure would or would not be encompassed by the term . . . .

The correct test for indefinite claim language is whether one of ordinary skill in the art would be confused as to the meaning of subject matter defined by the language at issue. *In re Kroekel*, 183 USPQ 610 (CCPA 1974). Applying this test demonstrates that the language at issue satisfies the requirements of 35 USC 112, ¶2.

As well known in the art, a protein's "tertiary structure"

> is the way in which the helices or sheets are folded or arranged to give the three-dimensional structure of the protein.

CancerWEB The On-line Medical Dictionary, 1998 (page attached, hereto, as Appendix I). The meets and bounds of maintaining essential three-dimensional (tertiary) protein structure were well known, as demonstrated by Zhang, et al., "Three-dimensional structure of human fibroblast growth factor, a structural homolog of interleukin 1β," *Proc. Natl. Acad. Sci. USA, 88*, 3446-50, 1991 (copy attached, hereto, as Appendix II). Effecting the "substitution so as "to essentially preserve" the tertiary structure, as recited in the instant claims, would have been readily understood by one skilled in the art. The attached printout of search results from the *Life Science Dictionary on the Internet* defines tertiary structure as "the three-dimensional structure of a polypeptide in its normal folded state" – this must imply that the tertiary structure of a *self-protein* is *the three-dimensional structure of the polypeptides of the self-protein in its normal folded state.*

Tertiary structure of a protein might of course be altered to some degree when one substitutes part of the amino acid sequence with a peptide containing a foreign T-cell epitope. On the other hand, such a substitution will be more or less "destructive", and in some cases it will have virtually

no effect at all on tertiary structure. Thus, if substitution results in the breaking of a disulfide bridge, this will most likely disrupt the tertiary structure, and the same is true if an α-helix or a β-sheet structure is disrupted or removed. Also, removal or introduction of a proline residue can have dramatic effect on tertiary structure. Finally, local changes in the degree of hydrophilicity of a protein may also influence its tertiary structure, since hydrophilic residues tend to be surface-exposed whereas hydrophobic residues tend to be buried inside the protein structure.

In contrast, substitution in flexible loop structures is not likely to impose dramatic changes in tertiary structure, and the same is true for substitutions in flexible C- and N-terminal sequences in proteins. This is a consequence of the fact that none of these types of structures normally contribute to the tertiary structure of a protein.

It is important to note that "preservation of immunogenicity" does not imply "preservation of overall tertiary structure" whereas "preservation of overall tertiary structure" does in fact imply "preservation of immunogenicity":

It is well-known from text books in the art of immunology (e.g., enclosed pages 176-85,from chapter 8 ("Immunogenicity and antigen structure") from the textbook edited by E. Paul, *Fundamental Immunology*,second edition, 1989, Raven Press, New York, discussed above.) that epitopes in a protein may be "assembled topographic" or "segmental", the first term designating epitopes comprised of amino acid residues from different parts of the primary sequence and the latter term designating epitopes comprised of a continuous subsequence of amino acids – it should be evident that the first type depends completely on tertiary structure, but also segmental epitopes may depend in part on the tertiary structure, which "presents" the segmental epitope in an immunologically favorable manner. Nevertheless, some immunogenic segmental epitopes are

virtually independent on the tertiary structure. As long as the amino acid sequence of a such a segmental epitope is left unaltered, it will preserve its immunological properties even if changes are imposed on the tertiary structure of the protein.

This is the reason that the technique of vaccinating with short peptides derived from larger proteins has been known to be feasible for a long time; these small peptides having no tertiary structure are nevertheless immunogenic and capable of inducing production of antibodies which cross-react with the polypeptide of which they are a part. The fact that immunization with short peptides (e.g. decapeptides) is effective should render clear that tertiary structure is unessential for immunogenicity of these peptides.

One object of the present invention is to preserve a maximum number of B-cell epitopes, cf. page 4, lines 27-29, in the present specification. Further, in the paragraph bridging pages 8 and 9 it is indicated that the introduction of T-cell epitopes should introduce minimal changes in the tertiary structure. Also, on page 10, lines 9-12, it is indicated that the tertiary structure should be minimally obscured. These objects are met by preserving the overall tertiary structure of a self-protein. By doing this, a maximum number of B-cell epitopes *are* preserved and this has as a number of consequences listed in the specification.

Hence, one cannot meaningfully state that because a derivative of a protein is immunogenic and can induce antibodies cross-reactive with that protein, then the derivative has preserved the tertiary structure of the protein. By doing so, one would, e.g., be stating that a decapeptide capable of inducing antibodies against a larger protein of which the decapeptide is part *has* a tertiary structure – this is simply contrary to the art definition of the term tertiary structure. (Cf. the attached

declaration by Dr. Paul Travers addressing the issue of tertiary structure versus conservation of immunogenicity.)

While *limitations* from the specification cannot be read into the claims, words in the specification are properly used during prosecution as an aid in *interpret existing claim limitations*. This distinction is examined in the decision *In re Donaldson Co. Inc.*, 29 USPQ2d 1845, 1850 (Fed. Cir. 1994).

> The Commissioner confuses [1] impermissibly imputing limitations from the specification with [2] properly referring to the specification to determine the meaning of a particular word or phrase recited in a claim.

Claims are to be given their broadest reasonable interpretation during prosecution, but the definition of a claim limitation given by the Examiner cannot be different than would be given by one of ordinary skill in the art. *In re Cartright*, 49 USPQ2d 1464 (Fed. Cir. 1999). Moreover, the Examiner's definition of a claim limitation cannot conflict with the definition given in the specification. *In re Zletz,* 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

As explained in the present specification, the salient object of Applicants' invention is to make an effective *vaccine* from a self-protein; that is, modify the self-protein (1) so it induces antibody production in the host of origin, i.e., as if it were a foreign protein, (2) without inducing harmful side effects often associated with introducing foreign proteins to induce antibody production (e.g. in vaccinations). Applicants accomplished this objective by self-protein modification, which replaces a naturally occurring sequence in the self protein with an antibody-inducing sequence ("peptide"), but only those naturally occurring sequences not appreciably involved in the self-proteins ability to fold upon itself into its tertiary structure, i.e., its naturally occurring 3-dimensional (crystal) structure (specification, pages 6-7).

A claim must be construed as a whole. *Ryko Manufacturing Co. v. Nu-Star, Inc.*, 21 USPQ2d 1053, 1056 (Fed. Cir. 1991). The limitation at issue actually reads *(emphasis added)*

> ... *said substitution being carried out so as to* essentially preserve the overall tertiary structure...,

with the referenced "substitution" being

> ...a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal ....

The importance of construing the language at issue within the context of the entire claim is readily apparent.

Taken in its entirety, the language "to essentially preserve the overall tertiary structure" amounts to a *proviso* clause; it excludes from the scope of "peptide fragment" any fragment containing an amino acid sequence critical to the self-[protein's ability to fold its sequence (primary) structure into its "tertiary structure," i.e., the self-protein's naturally occurring 3-dimensional structure. In other words, the "peptide fragment" substituted cannot be one that would prevent the recited purpose "to preserve the ... tertiary structure."

Moreover, applicants submit that the statement of rejection evidences an apparent misunderstanding as to how a claim term is evaluated for satisfaction of 35 USC 112, ¶2. The statement of rejection is concerned about what specific "changes to the tertiary structure" are "encompassed" by the claim term. This is a concern about the scope of the language at issue. As such, the inquiry has no bearing on whether the term is indefinite under §112, ¶2, since claim "breadth is not to be equated with indefiniteness." *In re Miller*, 169 USPQ 597, 600 (CCPA 1970).

Questioning "what deviations from the normal crystal structure would or would not be encompassed by the term" is a meaningless inquiry under §112, ¶2 of the Statute. It evidences

concern that not all "deviations" in crystal (3-dimensional or "tertiary") structure will fulfill the claim function. However, the purpose of the claims is not to exclude possible non-working embodiments - in the instant case, non-working deviations in "tertiary structure." As explained in the decision *In re Smythe*, 178 USPQ 279, 286 (CCPA 1973):

> As we have said before, it is almost always possible to so construe a claim as to have it read on non-working embodiments, In re Cook, 58 CCPA 1049, 1054, 439 F.2d 730, 734, 169 USPQ 298, 301 (1971), but the alternative of requiring an applicant to be so specific in his claims "as to exclude materials known to be inoperative . . . would result in claims which would fail to comply with 35 U.S.C. 112, second paragraph, because they would be so detailed as to obscure, rather than to particularly point out and distinctly claim, the invention. In re Meyers, 56 CCPA 1129, 410 F.2d 420, 161 USPQ 668 (1969), quoted with approval in In re Anderson, 471 F2d 1237, 176 USPQ 331 (CCPA 1973).

The "use of materials which might prevent achievement of the [claim] objective ... can hardly be said to be within the scope of the claims." *In re Geerdes*, 180 USPQ 789, 793 (CCPA 1974). While a patent applicant may so choose to limit his invention to a specific embodiment described in the specification, "it is not necessary to embrace in the claims ... all possible forms in which the claimed principle may be reduced to practice." *Smith v. Snow*, 294 U.S. 1, 11 (1935).

Therefore, applicants submit that the rejection under 35 USC 112, ¶2, is fatally flawed for failing to apply the correct legal standards in determining whether the claim language at issue is indefinite.

Claims were rejected under 35 USC 102(b) for allegedly being anticipated by WO92/05192 (Russell-Jones). Reconsideration of the rejection is respectfully requested.

Applicants submit that the rejection cannot be maintained because it is flawed, both legally and factually. The rejection is flawed, legally, because it relies on an incorrect interpretation of the

law with respect to anticipation. The rejection is flawed, factually, because it is based on clearly erroneous factually findings as to what subject matter the instant claims define with respect to what subject matter the applied reference (Russell-Jones) describes.

The instant claims most broadly (i.e., claim 26) define, as method steps (*emphasis added*), a

> . . . method for inducing antibody production in an animal *against a self-protein of that animal*, the method comprising, administering, to the animal . . . at least one . . . self-protein . . . modified by . . . substitution . . . with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal . . . .

In other words, the steps of the presently claimed method involve

1) starting with an animal's native, non-immunogenic protein ("self-protein"),

2) changing the protein to make it immunogenic to the animal, i.e., the *substitution* limitation, and

3) reintroducing the now-immunogenic "self-protein" back into the same animal from which it was derived, i.e., the "*administering*"/"*self-protein*" limitation,

for the purpose of "inducing antibody production in the animal."

To anticipate the instant claims, each and every claim limitation, as arranged in the claims, must be found in a single prior art disclosure. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 USPQ 253 (Fed. Cir. 1985). The absence from a prior art reference of a single claim limitation negates anticipation. *Kolster Speedsteel AB v. Crucible Inc.*, 230 USPQ 81 (Fed. Cir. 1986). A reference that discloses "substantially the same invention" is not an anticipation. *Jamesbury Corp.* The statement of rejection fails to apply these standards when comparing the instant claims with Russell-Jones for the purpose of determining novelty under §102(b).

Russell-Jones relates to, *inter alia*, making a vaccine for "administration to a host requiring immunization" (Russell-Jones, page 12, lines 6-7). The vaccine contains what the reference refers to as "complex," which is immunogenic and is made using (1) T-cell epitopes derived from the TraT protein of *E. coli*, in combination with (2) what the reference refers to as "immunogens" (Russell-Jones, abstract). The immunogen and T-cell epitope can be linked chemically, or expressed as a single fusion protein using DNA recombinant technology, to form the complex (Russell-Jones, abstract).

Russell-Jones defines "immunogens" very broadly; i.e., a molecule that one desires to use in order "to raise an immune response" (Russell-Jones, page 8, lines 36-38). The molecule (immunogen) can be immunogenic (i.e., capable of raising an immune response); but, typically it is a poorly immunogenic molecule, which becomes part of the immunogenic "complex" (Russell-Jones, page 8, line 36, through page 9, line 3).

Russell-Jones fails to anticipate the claims since each and every claim limitation, as arranged in the claims, is not found in Russell-Jones. *Jamesbury Corp., supra.* As a general proposition, §102(b) rejection cannot be maintained since it relies, overall, on combining different teachings found at different parts of the reference, in the absence of any express or implied teaching found in the reference to do so. The only way the statement of rejection can arrive at this combination is by using the instant claims a blueprint. It must be remembered that anticipation requires each and every claim limitation be found in the reference *as arranged in the claims. Jamesbury Corp., supra.* Various teachings scattered throughout the reference, which can be combined into a single embodiment only in hindsight, are not found in the reference *as arranged in the claims.*

In any event, even if there were a single embodiment in the reference representing the scattered teachings relied on in the statement of rejection, there would still be no anticipation; the instant claim limitations are not met by the teachings of the reference as alleged in the statement of rejection. Specifically, the reference does not describe

a) the *substitution* limitation," i.e.,

> . . . the modified self-protein .... containing a *substitution* of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal . . . [*emphasis added*]

and

b) the *administering/self-protein* limitation, i.e.,

> . . . *administering*, to the animal, an immunologically effective amount of an immunogenic composition comprising at least one modified *self-protein* . . . .

Absence of either one of these limitations from Russell-Jones negates anticipation. *Kolster Speedsteel AB, supra.*

As mentioned above, the *substitution* limitation involves replacing a sequence in the naturally occurring self-protein with, essentially, "an immunodominant T-cell epitope." This substitution changes the self-protein from an immuno-tolerated molecule to one which the immune system recognizes as "foreign," i.e., one which induces antibody production in the animal from which the original self-protein was derived.

The statement of rejection alleges that Russell-Jones meets the *substitution* limitation of the instant claims. The statement of rejection arrives at this conclusion through legal error; i.e., the rejection does not apply the correct legal standards for determining anticipation under §102(b).

The statement of rejection relies on two parts (teachings) of Russell-Jones as allegedly meeting the "substitution" limitation in the instant claims. The first part relied on is Russell-Jones "Example 5," pages 31-32 of the reference. The second part relied on is text found at page 9 of Russell-Jones.

Example 5 of Russell-Jones describes replacing the "suppressor regions" of gp120 with "more immunogenic sequences" (Russell-Jones page 31, lines 24-28). Example 5 of Russell-Jones may, indeed, involve some kind of substitution of one amino-acid sequence for another; but, it involves neither (i) a "self-protein" nor (ii) replacing a fragment of the "self-protein," as presently claimed.

Contrary to describing a "self-protein," the particular "immunogen" in which the substitution occurs in Example 5 is a protein foreign to an animal; it is a protein found in the AIDS HIV virus, i.e., "gp120 . . . an immunodominant external envelope protein of HIV" (Russell-Jones page 31, lines 22-23). The gp120 protein of the AIDS virus is no animal "self-protein," as that term is used in the instant specification and claims. The instant specification defines a *self-protein* as "an individual's own proteins," against which "individuals do not normally harbor autoantibodies" (specification, page 1 last complete paragraph). Since this is the definition of the term provided in the specification, the examiner must use this definition in construing the claims for comparison with the prior art.

> When the applicant states the meaning that the claim terms are intended to have, the claims are examined with that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art.

Zletz, 13 USPQ2d at 1322. Moreover, claim terms need not be "conventional" in the art, since a patent applicant is entitled to be his ow lexicographer. *In re Castaing*, 166 USPQ 550 (CCPA 1970).

The statement of rejection argues that the teachings of Russell-Jones Example 5 are "not limited to gp120," relying on the reference description: "Using recombinant DNA technology, the 'suppressor regions' in a number of prospective vaccine proteins including gp 120 . . ." (Office action, page 5). Reliance on the quoted teachings of Russell-Jones is misplaced, since the description does not meet the claim "substitution" limitation. To anticipate the claim, each claim limitation must "*identically* appear" in the reference disclosure. *Gechter v. Davidson*, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997) (*emphasis added*). The phrase "a number of prospective vaccine proteins" is not identical to a "self-protein" as presently claimed. Moreover, it does not even suggest a "self-protein"; since the only example is a protein foreign to an animal – an HIV virus protein – any suggestion would be for another foreign protein.

Secondly, not only is there no teaching in Example 5 of a self-protein but, more importantly, there is no teaching or suggestion for the type of "substitution," as defined in the instant claims. The passage relied on from Example 5 of the reference, at best, gave the skilled artisan a procedure to be applied to "prospective vaccine proteins including gp120." While the skilled artisan may have gained sufficient knowledge to apply the teachings of Example 5 to "prospective" proteins, "that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there." *Motorola Inc. v. Interdigital Technology Corp.*, 43 USPQ2d 1481, 1490 (Fed. Cir. 1997). Neither *gp120* nor *prospective vaccine proteins including gp120* describes a "self-protein" as used in the instant claims; if the claim limitation does not "identically appear" in the reference, there is no anticipation. *Gechter*, 43 USPQ2d at 1032.

With respect to the disclosure at page 9 of Russell-Jones, the statement of rejection alleges that the reference's teaching to modify the "fusion protein" meets the "substitution" limitation of the instant claims. Reliance is, again, misplaced.

At page 9 Russell-Jones describes modifying the "complexes" of the invention using the same genetic engineering techniques that are used to make the "fusion proteins" of the invention. As mentioned, above, Russell-Jones teaches constructing DNA encoding a "fusion protein" as an alternative way of effecting the linked sequence <<immunogen–T-cell epitope>>, i.e., alternative to linking the T-cell epitope and immunogen using chemical means (i.e., synthesis). By selectively altering the nucleotide sequences in the DNA, Russell-Jones teaches, "it is possible to substitute codons [encoding] for amino acids with similar characteristics at places within a protein without affecting the activity of the molecule" (Russell-Jones, page 9, lines 34-37). This disclosure is not identical to the "substitution" limitation in the instant claims.

The alterations in peptide sequencing suggested by Russell-Jones (at page 9) do not even hint at substituting the T-cell-epitope sequence in place of a sequence falling within the immunogen part of the fusion protein. Russell-Jones suggests no more than altering the already constructed ("fusion protein") sequence <<immunogen–T-cell epitope>>. Once more, the disclosure relied on in the statement of rejection is found wanting, i.e., a limitation of the claims is absent from the disclosure, which negates anticipation. *Kolster Speedsteel AB, supra.*

It is worth recalling how "self-protein," as that term is used in the present claims, must be defined the analysis under §102(b). Since the specification expressly defines a *self-protein* as "an individuals own proteins," against which "individuals do not normally harbor autoantibodies"

(specification, page 1 last complete paragraph), this definition must be used in construing the claims for comparison with the prior art. *Zletz*, 13 USPQ2d at 1322. *Castaing, supra.*

According to the statement of rejection, the claim limitation to a "self-protein" is met by the definition for "immunogen" described by Russell-Jones, i.e., *"any molecule which it is desirable to use to raise an immune response"* (Office action, page 4, second, incomplete paragraph; *emphasis in original).* The fatal flaw in this argument is that *any molecule which it is desirable to use to raise an immune response* is not identical (literally or synonymously) to a "self-protein," so there is no anticipation. *Gechter, supra.* "Nothing prevents" the reference disclosure of *any molecule which it is desirable to use to raise an immune response* from being different than the claimed limitation, so there con be no anticipation. *Credle v. Bond*, 30 USPQ2d 1911, 1921 (Fed. Cir. 1994).

Moreover, the "immunogen" definition - "any molecule which is desirable to use to raise an immune response" - represents a large genus, within which genus the "self-protein" allegedly occurs. As such, the statement of rejection is legally in error, since the description of a genus, by itself, cannot support a rejection under §102 for anticipation of a species within the genus. *In re Kalm,* 154 USPQ 10 (CCPA 1967). *In re Ruschig,* 145 USPQ 274 (CCPA 1965). *In re Schaumann*, 197 USPQ 5 (CCPA 1978). *In re Petering*, 133 USPQ 275 (CCPA 1962).

The failure of a genus to anticipate a species is illustrated by the maxim "that which infringes if later anticipates if before." *Peters v. Active Manufacturing Co.*, 129 U.S. 530, 537 (1889). The genus does not anticipate the species since it does not, also, infringe it; other species of the genus could be used without infringing.

Furthermore, the rejection merely begs the question by arguing Russell-Jones covers any molecule which it is *desirable to use* to raise an immune response. That is, the statement of rejection

fails to explain where this *desirability* to use a self-protein to raise an immune response can be found in Russell-Jones. Invention involves both the *idea* of the invention as well as the *means* to achieve the desired idea, and both the idea and the means must be found in the prior art to negate patentability. *Oka v. Youssefyeh,* , 7 USPQ2d 1169 (Fed. Cir. 1986). *In re Hoffman* 37 USPQ 222 (CCPA 1938). At best, all the rejection alleges is that the *means* to achieve the idea would have been known based on Russell-Jones.

For the foregoing reasons the "substitution" limitation recited in the instant claims is not identically described in Russell-Jones. A claim limitation being absent from the reference, anticipation is negated. *Gechter, supra. Kolster Speedsteel AB, supra.* Therefore, the rejection under 35 USC 102(b), based on Russell-Jones, cannot be maintained.

With respect to the *administering/self-protein* limitation on the instant claims, the statement of rejection appears to simply ignore it; in any event, the rejection does not allege where Russell-Jones describes *modifying a self-protein and reintroducing the modified protein into the same animal from which it was derived.* Therefore, on its face the rejection is fatally defective; i.e., even if everything alleged in the statement of rejection were correct, there still remain a claim limitation missing from Russell-Jones, which negates anticipation. *Kolster-Speedsteel AB, supra.*

Applicants do take note, however, of the allegation "virtually any self-protein is an immunogen, if it is administered to the host animal with an appropriate adjuvant" (Office action, page 4). This allegation does not indicate were such a disclosure is found in Russell-Jones. Furthermore, it is totally made in hindsight; Russell-Jones not only fails to disclose the *idea* - use a self-protein in a way to allegedly fit the definition of "immunogen" - the reference fails to disclose

the *means* to achieve the idea - administer the self-protein to the host animal with an appropriate adjuvant.

The rejection fails to explain how the reference describes the *idea* to render a self-protein from an animal immunogenic and return it to the same animal as a vaccine, except in hindsight; i.e., except in view of the teachings provided by *applicants' invention.* One of ordinary skill in the art would be hard pressed to find anything, whatsoever, in Russell-Jones to even suggest, let alone describe, *rendering a self-protein immunogenic and returning to the host animal.* To be novelty defeating, a reference must put the public in possession of the identical invention claimed. *In re Donahue*, 226 USPQ 619 (Fed. Cir. 1985). Russell-Jones, quite simply, fails to do this.

For the foregoing reasons the limitation "administering, to the animal, an immunologically effective amount of an immunogenic composition comprising at least one modified self-protein," recited in the instant claims, is not identically described in Russell-Jones. A claim limitation being absent from the reference, anticipation is negated. *Gechter, supra. Kolster Speedsteel AB, supra.* Therefore, the rejection under 35 USC 102(b), based on Russell-Jones, cannot be maintained.

The instant claims are limited to "administering, to the animal, an immunologically effective amount of an immunogenic composition comprising at least one modified self-protein." Russell-Jones does not describe this limitation as arranged in the instant claims and, therefore, the reference fails to anticipate the instant claims. *Kolster Speedsteel AB, supra.*

With respect to the issue of self-proteins, it is true that Russell-Jones teaches the use in humans of a vaccine including, e.g., FSH, LH, somatostatin, or inhibin, or fragments thereof. It cannot be denied either that these 4 proteins exist as self-proteins in humans. However, Russell-Jones *et al.* does not state that the immunogen used to raise antibodies against any of these sex

hormones is derived from the self version thereof. As already pointed out in the response to the first office action (and supported by the evidence filed therewith) it has been attempted a number of times to raise antibodies in animals against each and every of these antigens by using non-self versions as part of the immunogen.

The language of the presently pending claims is quite clear: It is required that the immunogen comprises a self-protein wherein has been made a (gentle) substitution with a foreign T-cell epitope containing amino acid sequence while at the same time preserving overall tertiary structure of the self-protein.

In the Office Action, the statement of rejection states that "...There is no teaching in Russell-Jones *et al.* that humans would be immunized with nonhuman modified luteinizing hormone, somatostatin, inhibin or FSH...". Applicants do *not* disagree with this statement. Applicants hope, however, that the Examiner will agree that there is absolutely no teaching in Russell-Jones *et al.* that "...humans *would* be immunized with *human* modified luteinizing hormone, somatostatin, inhibin or FSH" – in fact the Examiner himself states on 4, line 13, that LH, somatostatin, inhibin, and FSH e.g. *could* be self-proteins (he uses the wording "e.g.").

This is exactly our point: Russell-Jones *et al.* is silent when it comes to the discussion of the relation between the *source* of the immunogen and the *animal* to be vaccinated. Therefore, applicants believe it is improper when the statement of rejection reads into Russell-Jones *et al.* that this reference discloses vaccination with modified self-protein, in view of the fact that no clear and unambiguous disclosure of vaccination with modified self-proteins can be found.

At present, the Examiner seems to be of the opinion that the fact that e.g. LH *could potentially be* a self-protein implies that LH *is* a self-protein used in autovaccination according to

Russell-Jones *et al.* However, if one compares with e.g. organic chemistry it is well-established practice that a generic disclosure of e.g. "hydroxyheptane" *does not normally* anticipate a specific disclosure of "5-hydroxyheptane", even though hydroxyheptane *could potentially be* 5-hydroxyheptane. In the present case, inhibin *can be* human inhibin used in humans, but it could be inhibin from any other relevant species used for vaccination in humans.

Since a substantial part of prior art disclosures relating to vaccination with LH, FSH, inhibin and somatostatin disclose vaccination with non-self derived versions of these proteins, the skilled person would not interpret the teaching of Russell-Jones *et al.* as a teaching relating to vaccination with modified self-proteins.

The above view is supported by the Rule 132 declaration by Dr. Paul Travers, submitted herewith.

The statement of rejection also states that the abstract by Talwar *et al.* 1992 submitted by us with the latest response discloses the use of human hCG/tetanus toxoid as a vaccine in humans. This is not true, and the relevance of the reference as prior art is therefore dubious. The abstract clearly indicates that the immunogens used are *ovine* luteinizing hormone coupled to TT, a fusion construct between *ovine* LH and hCG coupled to TT, and a mixture of oLH/TT and hCG/TT. In all cases these antigens are coupled to TT. The animals vaccinated are bonnet monkeys. Hence, none of the antigens used are "self" in the vaccinated animals. At any rate, even if the reference by Talwar *et al.* had disclosed vaccination of humans with human hCG (which is, as correctly pointed out by the statement of rejection, in fact the case in another reference by Talwar), this would not remove the fact that numerous other references in the prior art disclose *vaccination of animals against self-proteins by using heterologously derived variants of these self-proteins.*

A further point is the fact that the abstract by Talwar *et al.* does not disclose immunization with hCG and a carrier alone. It is noted in Talwar *et al.* that oLH/TT in Bonnet monkeys induces antibody production against hCG and it is observed that this immune response is enhanced when instead using oLH-hCG/TT or a mixture of oLH/TT and hCG/TT. There is, however, no indication that hCG/TT would itself be an effective immunogen capable of inducing anti-hCG antibodies. Claim 26 of the present application requires that the method results in *induction* of antibody production against a self-protein. All what can be seen from Talwar *et al.* is that antibody production (induced by oLH) is *enhanced* (not induced) by the presence of hCG.

Russell-Jones *et al.* does not indicate whether self-proteins are used as immunogens or not. Hence, the skilled person reading Russell-Jones *et al.* would have to determine what kind of immunization scheme is discussed when immunization against LH, FSH, inhibin and somatostatin is suggested. Turning to the prior art, the majority of disclosures applicants have been able to locate disclose the use of non-self LH, FSH, inhibin and somatostatin. The statement of rejection has provided no indication of where in Russell-Jones *et al.* it should be indicated that autovaccination with FSH, LH, somatostatin or inhibin self-proteins is clearly and unambiguously taught.

With respect to the term "immunogen," the statement of rejection asserts that the teaching of Russell-Jones *et al.* relates to any molecule one would wish to vaccinate against. In this context, the statement of rejection has cited the passage on page 8, lines 36-38. However, the statement of rejection has disregarded the next sentence which states that the at least one immunogen typically will be "...a molecule which is poorly immunogenic, but immunogenic molecules are not excluded...". Russell-Jones *et al.* does therefore not refer to non-immunogenic molecules.

Applicants refer to the enclosed pages 182-185 from chapter 8 ("Immunogenicity and antigen structure") from the textbook edited by E. Paul, *Fundamental immunology*, second edition, 1989, Raven Press, New York, discussed above.

If considering the 1st full paragraph on page 184, it appears clearly that this *standard text book* defines self-proteins as being immunologically silent in the endogenous host. Something which is immunologically silent cannot constitute an immunogen.

It is of course true that most proteins, including self-proteins, can be rendered immunogenic if using strong adjuvants or other means of alerting the immune system (coupling to carriers for example). The question is, however, whether it is fair to consider the self-protein to constitute the immunogen in such a situation. In our opinion, it is the combination of the self-protein with the strong adjuvant which is the immunogen, not the self-protein itself. This viewpoint is supported by the enclosed results page from the Biotech Online Dictionary, where the search was made for the term "immunogen". The definition given of the term is "a substance which is capable of inducing production of antibodies" However, a self-protein is normally not capable of inducing antibody production in the endogenous host; *i.e.* a self-protein is not an immunogen in the endogenous host – it is necessary to provide something more (e.g. an adjuvant or a carrier) before an immunogen is present in the autologous host. This viewpoint is also supported by the declaration by Paul Travers.

At any rate, Russell-Jones *et al.* does not in any way point specifically to the use of Trat epitopes for inducing immunity against non-immunogenic proteins, let alone self-proteins.

Concerning use of "substitution," first of all, the disclosure in Example 5 of Russell-Jones *et al.* relates to the substitution of *suppressor regions* with Trat peptides; this is evident from page

31, lines 25-28, and page 32, lines 7-10, and the rationale behind this approach is to remove immunosuppressing regions of a foreign polypeptide (gp120). What is done in Russell-Jones *et al.* is therefore to substitute a region in a (foreign) protein which causes an undesired immunosuppressive effect. The choice of the substitution strategy suggested in Example 5 is therefore a *need* to modify the amino acid sequence of gp120, because that amino acid sequence includes an *immunosuppressing region.*

Concerning the general applicability of this approach, Russell-Jones *et al.* merely states that it can be used in a number of prospective vaccine proteins *having suppressor regions* (cf. page 32, lines 7-10, sentence cited by the statement of rejection) – Russell-Jones does not point to any feasibility in using the approach on proteins which *do not* have suppressor regions. On the contrary, since Russell-Jones *et al.* points out that the strategy can be used in prospective vaccine proteins *having* suppressor regions, it seems that this feature of the prospective vaccine protein is mandatory according to Russell-Jones *et al.*

As stated in the attached declaration by Dr. Paul Travers, suppressor regions as described by Russell-Jones *et al.* are not generally known from self-proteins.

In fact, if the skilled person should attempt to substitute gp120 with a self-protein in Example 5 of Russell-Jones *et al.*, he would in order to follow the teaching of Russell-Jones *et al.* have to substitute *a suppressor region* with a Trat epitope.

First of all, it would normally be impossible to find such *an immunologically disadvantageous region* in a self-protein, hence no need to delete any amino acids in the self-protein. Second, an essential feature of the presently claimed invention is that the substitution must not interfere significantly with the tertiary structure of the original protein. Such a teaching cannot

be extracted from Russell-Jones *et al.* There is absolutely no guarantee that the substitution of a suppressor region of a protein will ensure preservation of overall tertiary structure compared to the native protein – Russell-Jones *et al.* provides no indications or warnings to this effect.

Furthermore, the substitution suggested in Russell-Jones *et al.* at the bottom of page 32 introduces a number of changes in the original polypeptide which do not seem to comply with the requirement of the present invention that the overall tertiary structure must be essentially preserved. The suppressor region which is suggested deleted contains 4 positively charged amino acids (4 arginines) and 8 negatively charged amino acids (5 glutamic acid residues and 3 aspartic acid residues) and therefore the suppressor region has a net negative charge. The Trat peptide suggested inserted also contains 4 positively charged amino acids (2 histidine, 1 arginine, and 1 lysine) but only 1 negatively charged amino acid (a glutamic acid) and therefore the Trat peptide has an overall positive charge. Further, the suppressor region contains a proline in position 4 which is not present in the Trat peptide – the presence of a proline is well-known to introduce a bend in the amino acid chain due to the carboxy and amino groups being part of the same ring structure.

Finally, Example 5 in Russell-Jones *et al.* is *prophetic* The teaching of the example is not carried out but merely described as a possibility. There is hence no demonstration whatsoever that the suggested construct in Example 5 in Russell-Jones *et al.* does in fact provide the desired technical effect, *i.e.* increased immunogenicity of gp120.

Accordingly, applicants submit:

- Example 5 is the only place in Russell-Jones *et al.* which suggests *substitution* in a protein with a Trat peptide.

- Example 5 in Russell-Jones teaches a specific substitution strategy where a *suppressor region of a foreign protein* is substituted with a Trat peptide.
- Self-proteins do to the best of our knowledge not contain suppressor regions.
- Example 5 first and foremost requires substitution of a suppressor region, whereas there are provided *no considerations* vis-à-vis preservation of tertiary structure.
- Example 5 is prophetic and does not provide any demonstration that the modified gp120 is effective in providing improved immunogenicity of gp120.
- Russell-Jones *et al.* does not give any indication that the teaching of Example 5 would be applicable in proteins not containing suppressor regions, let alone in self-proteins.

Even when combining the teaching of Example 5 with the more general statement in Russell-Jones *et al.* on page 33, 1st paragraph, the skilled person could not conclude that example 5 could also relate to vaccination of an animal with modified self-proteins of that animal. The statement on page 33 merely indicates that the vaccines of the invention are useful in humans but this does not indicate that the immunogen is prepared from human material (example: a tetanus vaccine is effective in humans, but Clostridium tetanii and its proteins are not of human origin, and in Russell-Jones *et al.* it is suggested to prepare a gp120 based vaccine for human use – gp120 is not a self-protein in humans).

Finally, the statement of rejection states that "Applicant has provided no evidence that the Example is not enabled."

It is submitted that the statement of rejection must provide evidence that a cited reference is *relevant*. The fact that applicants have been able to find not even a single later reference which

demonstrates the utility of the anti-HIV approach suggested in Russell-Jones *et al.* must imply (or at least provide a very strong indication) that this technology lacks enablement - in view of the seriousness of AIDS one would expect that a successful immunization against HIV using the approach of Example 5 would have been reported in at least one scientific journal in the period between 1992 and 2000. Further, it must be emphasized once again that Example 5 in Russell-Jones *et al.* is prophetic. There is absolutely no indication in the example that the strategy proved successful.

Applicants therefore respectfully request that the Examiner demonstrates the relevance of the cited part of the reference. If it cannot be demonstrated by the Examiner that the approach in Example 5 in Russell-Jones has at least proved successful in improving the immunogenicity of gp120, applicants hold that the teachings in the Example cannot anticipate "substitution in a self-protein which preserves tertiary structure of the self-protein".

At any rate, it is difficult to see how applicants should be capable of providing direct evidence that Example 5 in Russell-Jones *et al.* is *non-enabling*, since this would at least entail a vaccination study in a suitable animal model.

As all of the points mentioned above are addressed in the enclosed declaration by Paul Travers, applicants submit it must be concluded that:

- Russell-Jones *et al.* does not teach vaccination with modified proteins in an animal where the unmodified protein is "self".
- Russell-Jones *et al.* does not teach substitution with an immunodominant T-cell epitope in a self-protein.

- Russell-Jones *et al.* does not teach preservation of overall tertiary structure of a self-protein.

In contrast, the present invention *requires*:

- Vaccination with modified proteins in an animal where the unmodified protein is "self".
- Substitution with a T-cell epitope in a self-protein.
- Preservation of overall tertiary structure of a self-protein.

It is therefore respectfully submitted, that it is improper to reject the present disclosure as being anticipated by the disclosure in Russell-Jones *et al.*

Claims were rejected under 35 USC 103 for alleged obviousness based on Russell-Jones (cited in the rejection for alleged anticipation) combined with WO93/05810 (Hellman) and prior art allegedly described in the present specification at page 18, last paragraph. Reconsideration of the rejection is respectfully requested.

As an initial matter, in the event the Examiner is not aware, a United States patent corresponding to Hellman has issued, i.e., U.S. Pat. No. 5,653,980, granted August 5, 1997. This US patent shows on its face a §102(e) date of April 1, 1993.

Applicants, also, take note of the Protest filed under Rule 291(a), on June 16, 2000. The protest relies on the same Hellman reference (WO93/05810) cited in the instant rejection under §103. The Protest is addressed further, *infra*.

The rejection for alleged obviousness can not be maintained for the same reasons that the rejection for alleged anticipation can not be maintained. That is, the obviousness rejection relies on the teachings of Russell-Jones in the same manner as the anticipation rejection relies on the teachings

of this reference, and nothing in the secondary reference, or alleged disclosure of prior art in the instant specification, cures the fatal deficiency in Russell-Jones. Specifically, nothing in the secondary reference or in the alleged prior art described in the instant specification, would have motivated one of ordinary skill in the art to modify Russell-Jones to

1) effect, as presently claimed,

> . . . the modified self-protein .... containing a *substitution* of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal . . . [*emphasis added*]

2) followed by

> . . . *administering*, to the animal, an immunologically effective amount of an immunogenic composition comprising at least one modified *self-protein* [*emphasis added*] . . . .

An analysis for obviousness under §103 is similar to an analysis for anticipation under §102 in that "all limitations of a claim must be considered in determining the claimed subject matter as is referred to in 35 U.S.C. 103 and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982). In the instant case, the "substitution" limitation of the instant claims defines over the art relied on in the statement of rejection under §103. Therefore, the §103 rejection is in error. *Murphy*.

As mentioned above, the Protest relies on the same Hellman reference of record. The Protest argues that Hellman anticipates the invention (supposedly) claimed by Applicants. However, the protest relies on teachings in the Hellman reference, which were held non-enabling by the U.S. Examiner during prosecution of the U.S. application corresponding to the WO '810 reference, i.e., the application that matured into the above mentioned US Pat. No. 5,653,980.

During prosecution of Hellman's corresponding US application, the patent examiner held that the application (identical to the WIPO counterpart) sufficiently enabled only an invention containing "the entire CH2-CH3 domains of human IgE or peptides corresponding thereto" (Office Action, dated Oct. 12, 1994, p. 7, U.S. Patent Appln. No. 196,277). The Patentee conceded this point to the Examiner in order to obtain the patent, i.e., by canceling from the claims subject matter covering any "mutated form" of the constant CH2-CH3 domains. The disclaimed subject matter (that is, subject matter admittedly non-enabling) included the "heavily mutated form" described at page 5, lines 29-30, of the corresponding WO '810 publication. This same "heavily mutated form" of the CH2-CH3 domains held non-enabling by the Examiner is the description at page 5, lines 29-30 of the WO '810 reference on which the protest relies in its argument for alleged anticipation. Since the reference is non-enabling in this respect, there can be no anticipation. *Donahue, supra.*

Besides being a fatal flaw in the protest's argument, the lack of enablement is fatal to the obviousness rejection of record. According to the statement of rejection, "Hellman teaches that modulation of self proteins responsible for manifestations of a particular disease can be achieved using self molecules that contain T helper epitopes" (Office Action, p. 6, lines 4-6 from the bottom of the page). As explained above, the U.S. Patent Examiner held that enablement provided by Hellman's identical US counterpart was limited to non-mutated forms, i.e., only embodiments that contained the constant CH2-CH3 domains of human IgE or peptides containing these domains.

Therefore, contrary to the statement of rejection, Hellman does not teach "modulation of self protein molecules," because the reference lacks enablement for any such modulation. Where the reference description relied upon to support an obviousness rejection is not enabled by the reference, the obviousness rejection cannot be maintained. *Ex parte Naujoks*, 17 USPQ2d 1537 (BPA&I

1989). To reject a claims for obviousness under §103 based on modifying the teachings of a reference, existence in the prior art of a reason (motivation) to effect the modification is not, by itself, sufficient to sustain the initial burden on the PTO; the "record" must show

> . . . that it would also have been obvious *how* this [modification] could be achieved . . . . Obviousness . . . must not be judged by hindsight, and a "little modification" can be a most unobvious one.

In re Irani, 166 USPQ 24, 27 (CCPA 1970) (*emphasis in original*).

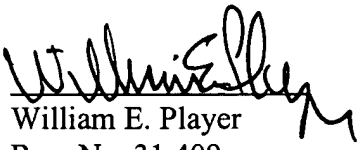
Moreover, it should be noted that the term "overall tertiary structure" of a protein, as discussed in detail above, means the 3-dimensional structure of a protein in its normal folded state. The fact that Russell-Jones *et al.* suggests the insertion of Trat peptides into proteins so as to preserve their immunogenicity *does therefore not imply* that the tertiary structure of these proteins is preserved, cf. also the declaration by Paul Travers.

Neither Russell-Jones nor Hellman go into any discussion of special advantages in using the presently claimed substitution approach. The approach is merely suggested in Russell-Jones in order to remove suppressor regions of foreign proteins.

However, as evidenced by present Example 5, the immune response induced by using the presently claimed approach it is accomplished to achieve *an earlier onset* and the provision of *a higher titre of antibodies* than by the traditional carrier protein approach. Furthermore, the vaccines of the present invention are also less allergenic than carrier protein containing vaccines and a higher number of epitopes are displayed because the present invention does not result in epitope shielding by the carrier moiety. These technical effects of the present invention are neither taught nor suggested in the prior art on record.

Favorable action is requested.

Respectfully submitted,

By: 
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